Appearance of Early Venous Filling During Intra-Arterial Reperfusion Therapy for Acute Middle Cerebral Artery Occlusion

A Predictive Sign for Hemorrhagic Complications

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Background and Purpose—The purpose of this study was to evaluate the correlation between appearance of angiographic early venous filling during intra-arterial reperfusion therapy and posttherapeutic hemorrhagic complications.

Methods—For the past 7 years, 104 patients prospectively underwent superselective local angiography via a microcatheter before and during intra-arterial reperfusion therapy for acute middle cerebral artery occlusion to evaluate the presence or absence of early venous filling. In principle, reperfusion therapy was discontinued just after appearance of early venous filling for fear of hemorrhage. There were 2 types of early venous filling: early filling of the thalamostriate vein from the lenticulostriate arteries and that of the cortical vein from the cortical arteries.

Results—Among these 104 patients, 31 (29.8%) had early venous filling: 19 had early filling of the thalamostriate vein, and the other 12 had early filling of the cortical vein. Eight of the 19 patients (42.1%) and 2 of the 12 patients (16.7%) had massive hematoma with neurological worsening, whereas only 1 of the 73 patients (1.4%) without early venous filling had massive hematoma. There was a significant correlation between early venous filling and massive hematoma in both the deep ($P<0.0001$) and superficial ($P=0.0019$) middle cerebral artery territories. The sensitivity and specificity of the presence of early venous filling as an indicator of parenchymal hematoma were 71% and 83%, respectively. None of the 31 ischemic areas with early venous filling could escape cerebral infarction.

Conclusions—Appearance of early venous filling may indicate irreversible brain damage and may be a predictive sign for parenchymal hematoma. (Stroke. 2004;35:893-898.)

Key Words: early venous filling ■ hemorrhagic transformation ■ stroke ■ middle cerebral artery ■ thrombolysis

When deciding whether to perform reperfusion therapy, the most important issue is to evaluate tissue viability and risk of hemorrhagic complications. Recent development of diffusion-weighted MRI (DWI) has enabled us to delineate damaged brain tissue easily from the early period of ischemia. Therefore, evaluation of tissue viability has become easier, and hypoperfusion areas without DWI-positive lesions, so-called diffusion-perfusion mismatch areas, are reported to be the best candidate for reperfusion therapy. However, DWI-positive lesions reflecting cytotoxic edema do not always result in hemorrhage after reperfusion therapy. When ischemic injury is limited to cytotoxic edema without endothelial damage, successful reperfusion therapy may be performed without hemorrhage. To prevent hemorrhagic complications, evaluation of endothelial damage is needed. Parenchymal extravasation on postcontrast CT has been reported to be a useful finding reflecting the presence of some degree of endothelial damage. When contrast medium is administered intra-arterially into the ischemic core via a microcatheter, endothelial damage may be detected with greater sensitivity than in conventional intravenous contrast-enhanced CT scans. However, CT is not usually available in the angiography room, and angiographic evaluation of endothelial damage may be more desirable.

Early venous filling, which is a well-known angiographic sign often seen in the ischemic brain tissue, may also reflect some degree of endothelial damage. When contrast medium is administered intra-arterially into the ischemic core via a microcatheter, endothelial damage may be detected with greater sensitivity than in conventional intravenous contrast-enhanced CT scans. However, CT is not usually available in the angiography room, and angiographic evaluation of endothelial damage may be more desirable.
Subjects and Methods

Patients
Since 1993, we have performed reperfusion therapy in 155 patients with acute MCA occlusion; 123 of them were treated with intra-arterial reperfusion therapy. For the past 7 years, to evaluate whether the lenticulostriate arteries (LSAs) are involved in ischemia and early venous filling has already appeared, 104 of these 123 patients underwent superselective local angiography with a microcatheter advanced just proximal or distal to the occlusion site and were enrolled in this study. Although we did not set a rigid therapeutic time window, almost all patients were treated within ~6 hours.

An initial CT scan was obtained just after admission for all patients with a Quantex RX (Yokogawa Medical Systems) with a section thickness of 10 mm. The initial pretherapeutic CT reading was performed by 2 or 3 neurosurgeons on duty to exclude patients with early CT signs on less than one third of the MCA territory. Intraparenchymal early CT signs, ie, obscuration of the margin of the lentiform nucleus, loss of the insular ribbon, and cortical effacement, were assessed. After the initial CT scan, all patients underwent cerebral angiography and were confirmed to have MCA occlusion. Before initiation of intra-arterial reperfusion therapy, a microcatheter was introduced just proximal or distal to the thrombus, and local angiography was performed to assess the presence of LSA involvement and early venous filling. Angiographic sites of arterial occlusion were divided into 3 types: (1) MCA trunk occlusion with LSA involvement, (2) MCA trunk occlusion without LSA involvement, and (3) M2 occlusion without LSA involvement. The M2 occlusions with short MCA trunk were considered to be a type 1 occlusion when a part of the LSA originated from the occluded M2 portion.

Pretherapeutic neurological status was evaluated with National Institutes of Health Stroke Scale (NIHSS) scores just before treatment.

Early CT Sign
Intraparenchymal early CT signs were reevaluated by 3 neurosurgeons (S.N., T.I., T.Y.) together. They knew only the side of hemiparesis, and CT images were read in an unblinded fashion. The purpose of the present study was not to evaluate the detection rate of early CT signs by blinded reading but rather to investigate the correlation of pretherapeutic early CT signs and early venous filling during reperfusion therapy. To minimize false-negative or false-positive interpretations, the presence of early CT signs was considered when all 3 readers were in accord after discussion.

Early Venous Filling
Early venous filling was defined as angiographic early appearance of the venous structures from the arterial phase during superselective local angiography via a microcatheter. There were 2 types of early venous filling: early filling of the thalamostriate vein from the LSAs (Figure 1) and early filling of the cortical vein from the cortical arteries (Figure 2). Patients with the former type of early venous filling was called the perforator group; those with the latter, the cortical group.

Local angiographies were performed several times during intraarterial reperfusion therapy to assess the degree of recanalization, and early venous filling was also prospectively analyzed by 2 or 3 neurosurgeons during treatment. When it appeared, further treatment was discontinued in principle to prevent hemorrhagic complications.

Treatment
Until now, 3 types of intra-arterial reperfusion therapies have been performed: intra-arterial thrombolysis using urokinase and/or tissue plasminogen activator, direct percutaneous transluminal angioplasty, and treatment combining direct percutaneous transluminal angioplasty and thrombolysis. Details of these treatment procedures were described previously. Informed consent for examinations and treatments was obtained from patients or their family members.

Figure 1. Representative superselective local angiography via microcatheter showing early filling of thalamostriate vein (arrows) from LSAs.

Just before initiation of reperfusion therapy, 5000 U IV heparin was administered, and an additional 1000 U heparin was given at 1-hour intervals during the procedure.

Doses of urokinase ranged from 60 000 to 600 000 U, with 10 mL of saline per 60 000 U, in boluses. Doses of native tissue plasminogen activator ranged from 3.6 to 14.4 mg, with 10 mL of saline per 1.8 mg, in boluses.

Direct percutaneous transluminal angioplasty was performed with a Stealth angioplasty balloon catheter with a maximum diameter of 2.0 to 2.5 mm. The balloon catheter was advanced into the occlusion site and inflated to 2 atm initially and subsequently to 3 atm. Several inflations of 30 seconds each were performed until recanalization was established.

Posttherapeutic intravenous continuous infusion of 10 000 to 15 000 U/d of heparin was performed for 7 days only in cases of incomplete recanalization or residual severe stenosis without contrast extravasation on posttherapeutic CT. When complete recanalization was achieved or contrast extravasation was seen, posttherapeutic anticoagulation therapy was not performed.

Blood pressure during and after reperfusion therapy was controlled strictly below 160 mm Hg systolic and 90 mm Hg diastolic with calcium antagonists (nifedipine or nicardipine).

The degree of angiographic recanalization was evaluated by neurosurgeons in charge of the reperfusion therapy and graded according to Thrombolysis in Myocardial Infarction (TIMI) grades.

Complete recanalization (TIMI 3) was defined as normal
opacification of all occluded arteries. Partial recanalization (TIMI 2) was defined as recanalization of some but not all of the occluded arteries. TIMI 0 and 1 were considered to be no recanalization.

Follow-Up Evaluation
Posttherapeutic CT scans were performed just after reperfusion therapy, the next day, and 3 to 7 days after reperfusion therapy to assess the size and location of the infarcted areas and the presence of contrast extravasation or hemorrhagic transformations. Follow-up CT scans were evaluated by 2 or 3 neurosurgeons in charge of the reperfusion therapy. Posttherapeutic intraparenchymal hyperdense areas were defined as hemorrhages when they did not resolve until >24 hours later. Hemorrhagic transformations were subdivided into 3 types: (1) petechial hemorrhage with spotty and scattered hyperdense areas, (2) small hematoma with a homogenous hyperdense area <3 cm in diameter, or (3) massive hematoma with neurological worsening (symptomatic hemorrhage). When hyperdense areas had already disappeared the next day, they were considered to be contrast extravasation alone.

Clinical outcome was assessed with the modified Rankin Scale at 3 months after onset. Favorable outcome was defined as a score of 0 or 1.

Statistical Analyses
Continuous variables were analyzed by the Mann-Whitney U test; categorical variables were analyzed by χ² statistics. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by logistic regression analysis to evaluate the association of early venous filling with the risk of hemorrhagic transformations. We chose a value of P=0.05 as a level of statistical significance.

Results
Among 104 patients, 31 (29.8%) had angiographic early venous filling during reperfusion therapy, and the other 73 patients (70.2%) had no early venous filling. Baseline characteristics of these 2 groups with and without early venous filling are shown in Table 1. There were no significant differences in age, sex, angiographic occlusive site, pretherapeutic NIHSS, degree of recanalization, methods of reperfusion therapy, doses of thrombolytic agents, and duration of ischemia between these 2 groups. The incidence of early CT signs showed a tendency to be higher in patients with early venous filling, although a statistically significant difference was not proved (P=0.0815). On the other hand, there were significant differences in the incidence of posttherapeutic contrast extravasation (P<0.0001) and hemorrhagic transformations (P<0.001) between these 2 groups, resulting in a significantly lower rate of favorable outcome in patients with

| Table 1. Baseline Characteristics of the 2 Groups With and Without Early Venous Filling |
|---------------------------------|---------------------------------|-----------------|---|
| Age, y                         | 70.5±8.4                        | 68.3±10.6       | NS |
| Sex, n (%)                     |                                 |                 |   |
| Male                           | 19 (61.3)                       | 41 (56.2)       | NS |
| Female                         | 12 (38.7)                       | 32 (43.8)       | NS |
| Occlusive site, n (%)          |                                 |                 |   |
| M1 with LSA                    | 18 (58.1)                       | 29 (39.8)       | NS |
| M1 without LSA                 | 4 (12.9)                        | 22 (30.1)       | NS |
| M2                              | 9 (29.0)                        | 22 (30.1)       | NS |
| Recanalization, n (%)          |                                 |                 |   |
| Complete (TIMI 3)              | 5 (16.1)                        | 31 (42.5)       | NS |
| Partial (TIMI 2)               | 12 (38.7)                       | 23 (31.5)       | NS |
| None (TIMI 1 and 0)            | 14 (45.2)                       | 19 (26.0)       | NS |
| Treatment, n (%)               |                                 |                 |   |
| Thrombolysis                   | 22 (71.0)                       | 46 (63.0)       | NS |
| Direct PTA                     | 5 (16.1)                        | 7 (9.6)         | NS |
| Both                           | 4 (12.9)                        | 20 (27.4)       | NS |
| Doses                          |                                 |                 |   |
| UK, ×10⁴ U (n)                 | 20.7±12.4 (19)                  | 18.2±11.6 (37)  | NS |
| tPA, mg (n)                    | 7.2±4.1 (18)                    | 6.8±1.1 (40)    | NS |
| NIHSS                          | 15.5±4.2                        | 14.7±3.2        | NS |
| Duration of ischemia, h        | 3.9±1.58                        | 3.7±1.54        | NS |
| Positive early CT signs, n (%) | 26 (83.9)                       | 49 (67.1)       | NS |
| Contrast extravasation,* n (%) | 29 (93.5)                       | 48 (65.8)       | <0.0001 |
| Hemorrhagic transformations,* n (%) | 19 (61.3)                     | 15 (20.5)       | <0.0001 |
| Favorable outcome,* n (%)      | 7 (22.6)                        | 43 (58.9)       | <0.001 |

PTA indicates percutaneous transluminal angioplasty; UK, urokinase; tPA, tissue plasminogen activator; duration of ischemia; time from onset to termination of treatment.

*χ² test.
early venous filling. None of the 31 ischemic areas with early venous filling could escape cerebral infarction. Furthermore, 29 (93.5%) were associated with posttherapeutic contrast extravasation, suggesting that appearance of early venous filling may indicate irreversible brain damage with some degree of disrupted blood-brain barrier damage.

### Early Venous Filling and Hemorrhagic Transformations

The correlation between early venous filling and hemorrhagic transformations is shown in Table 2. The rates of total hemorrhagic transformations and symptomatic hematoma were 32.7% (34 of 104) and 10.6% (11 of 104), respectively. These rates in patients with early venous filling were 61.3% and 32.3%, whereas rates in those without early venous filling were 20.6% and 1.4%. There were significant differences in these rates between the 2 groups with and without early venous filling \((P<0.0001, \chi^2\) test). Compared with patients without early venous filling, those with early venous filling had a significantly higher risk of symptomatic hemorrhage \((P<0.0001, \chi^2\) test; OR, 34.48; 95% CI, 4.15 to 250).

In view of the prediction of parenchymal hematoma, the predictive values of early venous filling were as follows: sensitivity, 17 of 24 (71%); specificity, 66 of 80 (83%); positive predictive value, 17 of 31 (55%); negative predictive value, 66 of 73 (90%); and overall accuracy, 83 of 104 (80%) (Table 3).

There were 7 patients with failure of strict blood pressure control. Four of them had early venous filling, and all 4 died as a result of massive hematoma. The other 3 patients had neither early venous filling nor massive hematoma.

Among 31 patients with early venous filling, 19 had early filling of the thalamostriate vein (perforator group), and the other 12 had early filling of the cortical vein (cortical group). In the perforator group, the rates of total hemorrhagic transformations and symptomatic hematoma were 68.4% and 42.1%, respectively, whereas in the cortical group, those rates were 50.0% and 16.7%. Subgroup analyses also demonstrated that there were significantly higher risks of hemorrhagic transformations in both the perforator \((P<0.0001, \chi^2\) test) and cortical \((P=0.0019, \chi^2\) test) groups compared with the control group without early venous filling. The presence of early venous filling was associated with increased risks of symptomatic hemorrhage in both the perforator \((P<0.0001, \chi^2\) test; OR, 52.63; 95% CI, 5.95 to 500) and cortical \((P=0.0078, \chi^2\) test; OR, 14.49; 95% CI, 1.19 to 166.67) groups.

The rate of symptomatic hemorrhage showed a tendency to be higher in the perforator group than in the cortical group, although a statistically significant difference was not proved \((P=0.14)\).

### Illustrative Cases

A 69-year-old man was admitted to our hospital because of sudden onset of right hemiplegia. CT scan on admission 1 hour after onset revealed only slight obscuration of the left posterolateral part of the lentiform nucleus (Figure 3A), and angiography demonstrated left MCA trunk occlusion with LSA involvement. Superselective local intra-arterial thrombolysis with 3.6 mg tissue plasminogen activator failed recanalization. During thrombolysis, however, early filling of thalamostriate vein appeared (Figure 1), and further thrombolytic therapy was discontinued. Posttherapeutic blood pressure could not be controlled appropriately. The next day, follow-up CT scan disclosed massive hematoma in the left basal ganglia (Figure 3B).

### Discussion

In our study, the rates of total hemorrhagic transformations and symptomatic hemorrhage, defined as a massive hematoma with neurological worsening (32.7% and 10.6%), were within the range of those in the recent controlled clinical trials for acute ischemic stroke.\(^{13–15}\) More than half of the hemorrhagic transformations (55.9%) and most of the symptomatic hemorrhages (90.9%) occurred in patients with early venous filling, who accounted for only 29.8% of all patients.

Early venous filling has been reported to be a common angiographic finding in cerebral infarction.\(^7,8\) Early venous filling has been considered to reflect the rapid passage of the contrast material secondary to the marked vasodilatation as a result of ischemia rather than the existence of an actual bypass of blocked capillary beds with arteriovenous shunting. The appearance of early venous filling is an indication of increased local circulatory rate and represents a regional cerebral hyperemia, the so-called luxury perfusion.\(^16–18\)
though cerebral hyperemia may be seen also in the perifocal reversible areas around infarcts, early venous filling has been reported to be seen only in the ischemic core, almost in the infarcted areas.8 Unless contrast material flows into the ischemic area, early-filling veins will not be opacified. Therefore, they may not be seen in the initial angiogram and often appear in the course of interventional reperfusion therapy. They are often seen when local angiography is performed via microcatheter located near the occlusion site. We hypothesized that the appearance of early venous filling may be suggestive of irreversible ischemic damage and that reperfusion therapy for such a hyperemic brain tissue might be associated with significant risk of hemorrhagic complications.

Our present study has demonstrated that none of the ischemic lesions with early venous filling could escape cerebral infarction. Furthermore, among the 31 patients with early venous filling, posttherapeutic CT scan showed extravasation in 29 patients (93.5%) and hemorrhagic transformations in 19 patients (61.3%). These results suggest that the appearance of early venous filling may be a reliable sign of irreversible brain damage with endothelial injury. Although the positive predictive value of early venous filling as an indicator of parenchymal hematoma was low (55%), its sensitivity was relatively high (71%), suggesting that the appearance of early venous filling may be a predictive sign for hemorrhagic complications. Therefore, once early venous filling appeared during intra-arterial reperfusion therapy, some degree of hemorrhagic complications might be expected. The most important issue is to prevent symptomatic hemorrhage. In such instances, further treatment, particularly intra-arterial infusion of thrombolytic agents, should be discontinued, and strict blood pressure control should be performed to prevent symptomatic hemorrhage.

In our study, when the appearance of early venous filling was recognized during intra-arterial reperfusion therapy, we discontinued further treatment and tried strict blood pressure control. Nevertheless, no fewer than 32.3% of patients with early venous filling had symptomatic hemorrhage. Particularly, failure of strict blood pressure control resulted in symptomatic hemorrhage. Even if blood pressure were strictly controlled, it might be difficult to prevent symptomatic hemorrhage, particularly in patients with early filling of the thalamostriate vein from the LSAs. Compared with early filling of cortical vein, early filling of the thalamostriate vein may have a high risk of symptomatic hemorrhage, although a statistically significant difference was not proved. Although not significant, a lower recanalization rate may also partially account for the worse outcome in the early venous filling group.

On the contrary, considering that 90.9% of symptomatic hemorrhage occurred in patients with early venous filling and that only 1.4% of patients without early venous filling had symptomatic hemorrhage, the absence of early venous filling may be a reliable negative predictor of symptomatic hemorrhage. The specificity and negative predictive values of early venous filling as a negative predictor of parenchymal hematoma were also as high as 83% and 90%, respectively. Therefore, when early venous filling is not seen during intra-arterial reperfusion therapy, there may be little possibility of symptomatic hemorrhage.

Our study has some limitations. Because of the lack of multiple logistic regression analysis, it is unclear whether early venous filling is an independent predictor of hemorrhagic complications regardless of other clinical and imaging parameters. It is also remained unknown whether the time course of the appearance of early venous filling during intra-arterial reperfusion therapy may influence the occurrence of hemorrhagic complications.

In conclusion, when some intra-arterial reperfusion therapies were considered for acute MCA occlusion, the presence or absence of early venous filling should be confirmed by performing local angiography via microcatheter located near the occlusion site. If early venous filling is recognized during
reperfusion therapy, particularly in the deep MCA territories, a considerable high risk of hemorrhagic complications should be expected. To prevent symptomatic hemorrhage, strict blood pressure control should be performed and further intra-arterial infusion of thrombolytic agents should be discontinued.

References
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